

A Comparative Study of Analgesic Effect of Intrathecal Neostigmine, Fentanyl and Combination of both as an Adjuvant to Intrathecal Bupivacaine and Bupivacaine Alone for Abdominal Hysterectomy

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Abstract: Relief of pain during surgery is the main aim of anesthesia. Any expertise acquired in this field should be extended into post operative period. Many options are available for the treatment of post-operative pain, including systemic analgesics (i.e., opioid and non opioid); and regional techniques. In this study opioid analgesic fentanyl and neostigmine which were injected in intrathecal space along with local anaesthetic agent hyperbaric bupivacaine 0.5% for operative and post operative pain relief in patients undergoing abdominal hysterectomy. The primary goal of this study was to determine whether the combination of fentanyl and neostigmine with intrathecal bupivacaine has better analgesic duration than fentanyl and neostigmine alone with intrathecal bupivacaine. Method: One hundred and sixty four patients of ASA physical status grade I and II, scheduled for elective Total Abdominal Hysterectomy under subarachnoid block were randomly allocated to four groups (n=41): Group A received 15mg bupivacaine intrathecally. Group B received 15mg bupivacaine plus 25 micrograms of fentanyl intrathecally. Group C received 15mg bupivacaine plus 25 micrograms neostigmine intrathecally. Group D received 15mg bupivacaine plus 25 micrograms neostigmine and 25 micrograms fentanyl intrathecally with total volume made upto 4.0ml with NS in each group. Result: Duration of analgesia in post operative period was group A (126.05±19.33 minutes), group B (208.2±15.74 minutes), group C (194.37±15.54 minutes), group D (290.8±20.24 minutes). Statistically significant difference in duration of post operative analgesia was found when group A was compared with other 3 groups. Duration of 2 segment regression was group A (79±11.64 minutes), group B (125±19.57 minutes), group C (125±7.85 minutes), group D (135±8.24 minutes). Statistically significant difference in duration of 2 segment regression was seen when group A was compared with rest of groups. Onset of motor block was also found to be similar in all the 4 groups. Onset of motor block was also found to be similar in all the 4 groups. Conclusion: The combination of intrathecal neostigmine and fentanyl with bupivacaine significantly prolonged post operative analgesia as compare to other three study groups.

Keywords: Fentanyl, Neostigmine, Postoperative analgesia

1. Introduction

Pain is a dehumanizing experience that destroys the soul. Pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage. Relief of pain during surgery is the main aim of anesthesia. Any expertise acquired in this field should be extended into post operative period. Severe post operative pain is a well known morbidity and causes distress to patients. Despite the introduction of new analgesics for pain relief, the advances of post operative pain relief still depends on the improvement in the delivery of existing drugs to the patients.

Many options are available for the treatment of post-operative pain, including systemic analgesics (i.e., opioid and non opioid); and regional techniques. Efficacy of intravenous opioids is typically limited by the development of tolerance or opioid related side effects. Intravenous opioids are commonly used for moderate to severe post-operative pain. Neuraxial and peripheral techniques can provide superior analgesia compared to systemic drugs. Spinal anesthesia, a common technique in anesthesia practice, has had a stormy course throughout its relative short history, especially in the first four decades from 1900-1940, having been exposed to alternating phases of enthusiasm, skepticism and even outright condemnation.

It was not until 1957 when Ekenstem synthesized bupivacaine and reported that it had long duration of action with low toxicity compared from lignocaine¹. Ekblom and Widman (1996) were the pioneer workers who employed bupivacaine for spinal analgesia and reported its low toxicity and long duration of action². It was further used by many workers for spinal and epidural blocks and they observed that bupivacaine was three to four times more potent and possessed longer duration of action than lignocaine.

The cholinergic pathway plays an important inhibitory pathway for pain modulation. Cholinomimetic drugs, including cholinergic receptor agonist and acetylcholinesterase inhibitor known to produce analgesia in various species. Neostigmine is a reversible acetylcholinesterase inhibitor quaternary ammonium compound used as cholinomimetic analgesic in human. Autoradiographic studies have revealed the presence of muscarinic binding sites in dorsal horn and reported the maximum concentration of choline esterase is located in substantia gelatinosa of spinal cord³. Intrathecal neostigmine prolongs the sensory and motor block induced by bupivacaine spinal anaesthesia and at the same time causes no haemodynamic or respiratory depression in intraoperative and post operative period.

In this study opioid analgesic fentanyl and neostigmine which were injected in intrathecal space along with local

anaesthetic agent hyperbaric bupivacaine 0.5% for operative and post operative pain relief in patients undergoing abdominal hysterectomy. The primary goal of this study was to determine whether the combination of fentanyl and neostigmine with intrathecal bupivacaine has better analgesic duration than fentanyl and neostigmine alone with intrathecal bupivacaine.

2. Materials and Methods

This prospective, randomised, double-blind, study was done at a tertiary care centre after the approval of the Institutional Ethical Committee and obtaining written informed consent from all patients. One hundred and sixty four patients of ASA physical status grade I and II, aged 30-50 years, scheduled for elective Total Abdominal Hysterectomy under subarachnoid block were randomly allocated to four groups ($n=41$): **Group A:** (Control group): Patients received 15mg bupivacaine intrathecally. **Group B:** Patients received 15mg bupivacaine plus 25 micrograms of fentanyl intrathecally. **Group C:** Patients received 15mg bupivacaine plus 25 micrograms neostigmine intrathecally. **Group D:** Patients received 15mg bupivacaine plus 25 micrograms neostigmine and 25 micrograms fentanyl intrathecally with total volume made upto 4.0ml with NS in each group. Patients excluded from the study were those who refused to give consent, ASA Grade III and IV, any deformity or local sepsis in spinal lumbar region, severe hypovolemia, increased intracranial pressure, any bleeding or coagulation abnormalities, patients receiving tranquilizers, phenothiazines, or other CNS depressants (including alcohol), any major pre-existing neurological, cardiovascular, metabolic, hepatic, respiratory or renal disease, history of allergy or hypersensitivity to any of the study drugs or concurrently being treated for nausea or vomiting, Hb < 10gm % and patients in whom spinal anaesthesia failed and general anaesthesia was required.

3. Procedure

All patients underwent a thorough pre anaesthetic checkup and were fasted for at least 6hrs before the procedure. After taking written informed consent patients were randomly allocated to one of the four groups using chit in the box method. All routine monitors were attached and preoperative baseline readings of NIBP, PR and saturation were noted. After securing an IV access using 18G intravenous cannula all patients irrespective of the group they belonged were preloaded with Ringer's Lactate 15ml/kg over 10mins. Under all aseptic precautions spinal anaesthesia was performed in the operating room at the L₃ – L₄ interspace, with the patient in the left lateral position using 25G Quincke spinal needle. A volume of 4.0 ml of drug was injected over 30 seconds without barbotage. The intrathecal drugs composition depended upon the group to which patient belonged. Patient was placed in supine position with a 15° head down tilt immediately after spinal injection to achieve level of block of T5-T6. An indwelling urinary catheter was inserted before the start of the operation. Intraoperative fluid management was done according to the blood loss and hemodynamic parameters. The drug combination was prepared by one anesthesiologist and was given by another experienced one who was blinded to the study drug used and did not take

further part in the study. Both patients and the observer were blinded regarding to the study drug or the group. Sensory block was assessed by the pinprick method bilaterally along the mid-clavicular line with a 25-gauge hypodermic needle at 2 min interval till the highest level of block was achieved and the required time was noted. The onset of sensory block was defined as the time from intrathecal injection of the study drug to the time taken to achieve T6 dermatomal level of sensory block. Regression of sensory block was defined as the time taken for the sensory block to regress by two dermatomal segments from the highest level achieved. Motor block was assessed according to the modified Bromage scale. The onset of motor block was defined as the time from intrathecal injection of the study drug to the time taken to achieve complete motor block (Bromage score-IV). Duration of motor block was the time elapsed from the maximum to the lowest Bromage score I-IV. Intraoperatively, monitoring of blood pressure, pulse rate, saturation and respiratory rate were done at 5 min interval. Hypotension was defined as a fall of mean arterial pressure (MAP) by more than 20% from baseline or a fall of systolic blood pressure below 90 mmHg and it was treated with incremental IV doses of mephentermine 5 mg and IV fluid as required. Bradycardia, defined as HR <50 bpm, was treated with injection atropine 0.6 mg IV. The post-operative pain and sedation level were assessed according to the VAS (0-10) and the 'four point sedation scale' (score 1 = spontaneous eye opening [awake and alert]; score 2 = drowsy, responsive to verbal stimuli; score 3 = drowsy, arousable to physical stimuli; score 4 = unresponsive), respectively, at 30-min interval upto 4 h and hourly thereafter till the request for first rescue analgesia.[5] Every patient received injection diclofenac 75 mg IV as rescue analgesic on VAS of 3. The time from intrathecal injection to first rescue analgesia (total duration of analgesia) was recorded and this was the end point of our study. We observed all patients for next 24 h regarding any complications such as nausea, vomiting, hypotension, bradycardia, respiratory depression and managed them accordingly.

Statistical analysis was performed with the SPSS, version 15.0 for Windows statistical software package (SPSS inc., Chicago, il, USA). The normality of the data distributions was evaluated using the Shapiro-Wilk test. Categorical data i.e. type of surgery and the incidence of adverse events (hypotension, bradycardia, respiratory depression, shivering, nausea, pruritis and headach) are presented as numbers (percent) and were compared among groups using Chi square test. P value <0.05 was considered statistically significant. Groups were compared for demographic data (age, weight), duration of surgery, time for two segment regression, VAS score, total duration of motor block and analgesia by analysis of variance (ANOVA), t-test. Probability was considered to be significant if less than 0.05. Data is represented as mean and standard deviation.

4. Results

All the groups were comparable with respect to age, weight, ASA status, type of surgery and duration of surgery [Table 1].

Table 1: Distribution of Demographic Variables

Variables	Group A	Group B	Group C	Group D
Number of patients	41	41	41	41
Age (Yrs)*	41.76±5.55	41.05±6.66	39.56±6.52	40.54±5.71
Weight (Kgs)*	53.51±9.1	54.02±5.21	52.22±6.40	52.56±5.04
Duration of Surgery (mins) *	51.66±9.64	50.46±9.73	48.98±13.15	49.59±12.72

* P > 0.05 (Non-Significant)

Table 2: Characteristics of Spinal Block

Variables	Group A	Group B	Group C	Group D
Number of patients	41	41	41	41
Onset of motor block [@] (mins)*	8.85±1.24	8.44±1.05	8.46±0.50	8.46±0.71
Total duration of Motor Block\$ (mins.)	114±10.07	121±13.52	115±6.62	126±6.1
Time for 2 segment regression (mins) %	79±11.64	125±19.57	125±7.85	135±8.24
Total duration of Analgesia (mins)#	126.05±19.33	208.2±15.74	194.37±15.54	290.8±20.24
Total no. of analgesia dose in 24 hours	3.51±0.51	2.39±0.49	2.54±0.50	1.76±0.49

[@] Bromage Grade III; ^{\$} Return to Bromage Grade II

* P > 0.05 (Non-Significant)

% Statistically significant difference between: group A was compared with group B (p=0.00), group C (p=0.0000) & group D (p=0.000).

Statistically significant difference between when group A was compared with group B (p=0.00), group C (p=0.000) & group D (p=0.000)

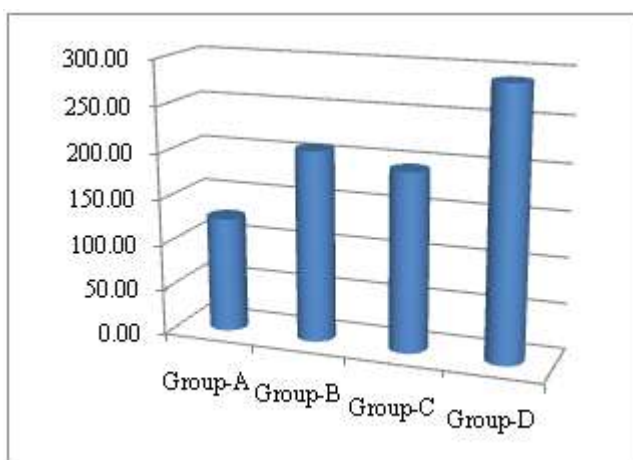


Figure 1: Comparison of Time to First Rescue Analgesia

Table 3: Incidence of Adverse Effects

Effects	Group A N(%)	Group B N(%)	Group C N(%)	Group D N(%)
Hypotension [‡] (p=0.0937)	2(4.8%)	5(12.2%)	7(17%)	11(26.8)
Bradycardia [‡] (p=0.09302)	2 (4.8%)	1(2.4%)	2 (4.8%)	2 (4.8%)
Respiratory depression [‡] (p=1.00)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Nausea, Vomiting [‡] (p =0.4284)	2 (4.8%)	3(7.3%)	6(14.6%)	5(12.2%)
Pruritus [‡] (p >0.05)	0 (0%)	3 (7.3%)	0(0%)	3(7.3%)

There were no significant differences regarding the incidence of perioperative adverse effects. There was no significant difference in number of patients experiencing episodes of bradycardia and hypotension (p>0.05)[‡]. None of the patients experienced respiratory depression or desaturation (p=1.00). In all the fentanyl using groups (B & D) patients reported pruritus i.e. three patients from the Group B and 3 patients from Group D. Two patients from the group A and three patients from group B, 6 patients from Group C (p=0.637)[‡] and five patients from group D reported post operative nausea and vomiting.

[‡]statistically insignificant difference (p>0.05) when compared with group A [Bupivacaine group(control)].

5. Discussion

It is well recognized that the post operative pain is being under treated and the conventional therapy of providing intermittent analgesics on patient demand is an ineffective method of pain relief. The routine use of regional anaesthesia for lower abdominals surgeries is associated with a short duration of analgesia post operatively which can be extended by i.m and iv. analgesics once patient experiences pain and demands for its relief. This causes intermittent and relatively ineffective analgesia, demands more patient care and provides least patient satisfaction. This problem is circumvented by giving analgesics prior to occurrence of pain. The pre-emptive mixing of analgesics with local anaesthetics for regional anaesthesia provides a better alternative. Considerable evidence exists to implicate a role for the cholinergic agonists and anticholinestrase agent in spinal inhibition of nociceptive transmission. Intrathecal neostigmine antinociception is secondary to acetylcholine release and action in spinal cord tissue. the intrathecal neostigmine, it causes dose dependent post operative analgesia by inhibiting the breakdown of acetylcholine in dorsal horn and spinal meninges and further, acetylcholine may cause analgesia through direct action on spinal cholinergic muscarinic receptors M1 and M2 and indirectly through stimulation of release of the second messenger nitric oxide in the spinal cord, whose mechanism of action is likely to include activation of second messengers such as cyclic guanosine monophosphate (cGMP)⁵. Muscarinic receptors have been identified in the spinal cord horn and intermediolateral cell column⁶. The changes in vital parameters of both cardiovascular and respiratory system by

different doses of neostigmine with bupivacaine was studied by De rosa⁴ and Minovsky⁷.

Intrathecal clonidine, fentanyl and neostigmine stimulate acetylcholine release from spinal cord "dorsal horn". Analgesic effect of all these are secondary to acetylcholine release in the spinal cord tissue. As reported in the study of Fared ahmed et al⁸. In our study mean Duration of analgesia was 290.8 minutes when bupivacaine with neostigmine and fentanyl were used. It was 194.37 minutes when bupivacaine with neostigmine were used and 208.2 minutes when bupivacaine with fentanyl was used and was 126.05 minutes when bupivacaine alone was used. Our result coincide with Lauretti et al⁹ in which the total duration of analgesia in combination group of neostigmine and fentanyl was 338 minutes. The total duration of analgesia in fentanyl group was comparable with Diana F Gabinsky et. Al¹⁰ in which the total duration of analgesia was 222±13.8 min. It is more as compared to Biswas B N et al¹¹ (183 ± 9 min) who used fentanyl 12.5 micrograms intrathecally. However it is less than Fared ahmed 2010 et. Al¹² (249.3±31.06). The total duration of analgesia in Group C is comparable with results of Shobhana gupta¹³ (183.9±3.36 min) who used neostigmine 50µg with hyperbaric bupivacaine.

Our study demonstrated a synergistic interaction of antinociceptive effect to the post-operative pain between neostigmine and fentanyl. Results showed that, neostigmine enhanced the analgesic effect of intrathecal fentanyl. Bupivacaine group reported total analgesia of 126.05 minutes while the combination of bupivacaine and neostigmine with fentanyl resulted in 290.8 minutes of post operative analgesia after abdominal hysterectomy. This is more than two times of bupivacaine alone group.

In our study the time for 2 segment regression was 79 minutes and 135 minutes in Bupivacaine alone Group and Bupivacaine – neostigmine– Fentanyl Group respectively. The 2 segment regression time in Group B was 125±19.57 min which is greater as compared to results of Harbhej Singh et al¹⁴ (93 ± 22 minutes).

In our study the time for The onset of motor block was 8.85±1.24 minutes, 8.44±1.05 minutes, 8.46±0.50 minutes, 8.46±0.71 minutes in Groups A, B, C and D respectively. There was no statistically significant difference among the study groups (p>0.05). Our study result coincides with Harbhej Singh et al¹⁴, Diana F Gabinsky et. Al¹⁰ and U Srivastava et al¹⁵.

In our study the duration of motor block was 114±10.07 minutes, 121±13.52 minutes, 115±6.62 minutes and 126±6.1 minutes in Groups A, B, C and D respectively. There was no statistically significant difference among the groups (p>0.05). Our result were comparable with study done by Harbhej Singh et al¹⁴ and Diana F Gabinsky et. al.¹⁰

Intramuscular Diclofenac (75 mg) was be given as rescue analgesic. The mean number of doses required in 24 hours was 3.51, 2.39, 2.54 and 1.76. However statistically insignificant (p>0.05), lesser dose was required in neostigmine and fentanyl combination group. The neostigmine and fentanyl combination decrease the demand

of rescue analgesia. Our result coincides with Lauretti et al⁹.

6. Conclusion

The combination of intrathecal neostigmine and fentanyl with bupivacaine significantly prolonged post operative analgesia as compared to control group as well as bupivacaine and fentanyl or neostigmine groups. However no significant difference was seen in the onset and duration of motor block in all four groups.

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